Appendix A: Interview Guide

The New York Academy of Sciences (The Academy) has commissioned RTI International[1] to conduct an economic study of the potential impact of recommendations from the (1) NIH Alzheimer's Disease Research Summit, (2) Ware Invitational Summit, (3) National Alzheimer's Project Act (NAPA) Advisory Council, (4) Global CEO Initiative on Alzheimer's Disease, and (5) The Academy's Alzheimer's Disease and Dementia Initiative (ADDI) to improve the national infrastructure supporting therapeutic research and development (R&D) on Alzheimer's disease and dementia (hereafter Alzheimer's). The study will estimate the value of stakeholders co-investing in precompetitive public-private partnerships to overcome common roadblocks.

As a starting point for our discussion, some of the recommendations from these organizations are:

- Better detect and monitor Alzheimer's disease, especially from its earliest clinical manifestations, and better predict treatment response (thus de-risking clinical development) by developing, validating, and standardizing a robust hierarchy of **biomarkers** and sensitive cognitive and functional assessment tools, elucidating relationships among biological and **cognitive markers**.
- Enable efficient learning about Alzheimer's drug and biomarker combinations – testing, analytically validating, and qualifying biomarkers as new drugs are tested – by implementing **adaptive clinical trial designs** modeled on I-SPY 2.
- Reduce the time and cost of enrolling volunteers for research studies and clinical trials by expanding longitudinal databases, or **registries,** with standardized demographic, genetic, biologic, cognitive, and environmental information on likely volunteers.
- Increase the likelihood that success in preclinical development will translate to success in clinical development (i.e., **de-risk clinical development**) by conducting translational research in a precompetitive commons through public-private partnerships (modeled on, e.g., the Structural Genomics Consortium and

[1] RTI International is a not-for-profit research institute located in Research Triangle Park, NC. Please see: www.rti.org

Arch2POCM, NHLBI's SMARTT Program, or NIAID's clinical and preclinical resources for researchers), advancing a greater diversity of novel therapeutic approaches and validated targets into clinical trials.

- Better understand the etiology and mechanisms of Alzheimer's and speed the translation of this knowledge into the clinic by establishing a network of comprehensive **Alzheimer's disease centers**, integrated with existing infrastructure and resources such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and NIA-funded Alzheimer's disease research centers.

The purpose of these interviews is to learn the opinions of scientists and managers involved in Alzheimer's R&D about the potential of these recommendations to reduce the time, cost, and risk associated with therapeutic development and speed the arrival of disease-modifying therapies for Alzheimer's. In advance, we appreciate you sharing your thoughts and opinions with us.

The information from this interview will be kept confidential; individual responses will not be shared. Only aggregated responses will be summarized and included in our final report to The Academy on August 31, 2013. Our findings will be published in *Annals of the New York Academy of Sciences* around the end of the year.

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Organization of the Interview Guide

A. Respondents' backgrounds
B. Baseline and counterfactual costs of Alzheimer's R&D
C. Changes in Alzheimer's R&D performance
D. Acceleration of disease-modifying therapies for Alzheimer's

A. Respondents' backgrounds

With a short discussion, we would like to get a sense of

1. who is speaking more from a research science perspective and who is speaking more from a marketing perspective (both are important to hear from, as some questions are geared more to the science and some more toward the marketing side)
2. whether experience is in Alzheimer's research, CNS, or other disease area
3. and how familiar respondents are with the recommendations (from the five organizations noted on p. 1) to improve Alzheimer's R&D infrastructure.

B. Baseline and counterfactual costs of Alzheimer's R&D

Average development costs per approved new drug (for all diseases, not Alzheimer's specifically) are estimated to be as follows:[2]

Table 1. Development costs per approved new drug ($millions).

	Biotech out-of-pocket ($millions)	Biotech capitalized ($millions)	Pharma out-of-pocket ($millions)	Pharma capitalized ($millions)
Preclinical	230	720	174	510
Phase 1	124	278	156	338
Phase 2	121	217	171	312
Phase 3	173	235	279	385
Total	**648**	**1,450**	**780**	**1,545**

[2] Joseph A. DiMasi and Henry G. Grabowski. 2007. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 27: 1–11. Note: costs have been adjusted for inflation using the GDP implicit price deflator.

The cost estimates in Table 1 are based on the estimates of transition probabilities in Table 2 and cycle times in Table 3.

In this section, we would like to

1. customize these cost estimates for Alzheimer's by adjusting the transition probabilities in Table 2 and the cycle times in Table 3 to reflect the **current environment with existing infrastructure** (Question 1) and then

2. estimate the potential impact of improved infrastructure on development costs by re-estimating the transition probabilities in Table 2 and the cycle times in Table 3 **as they might be in a new environment with better infrastructure as would exist if the recommendations above were fully implemented** 3 to 5 years from now (Question 2).

Question 1 In the **current environment with existing infrastructure**, what are the transition probabilities (Table 2) and cycle times (Table 3) for Alzheimer's disease-modifying drug candidates?

Question 2 In the **new environment with the recommended infrastructure**, what would be the transition probabilities and cycle times for Alzheimer's disease-modifying drug candidates? (A likely range of possibilities is fine.)

Numbers **[in brackets]** are based on preliminary interviews.

From your perspective, do these numbers seem reasonable? too high? too low?

(Please provide AD-specific numbers)

Table 2. Transition Probabilities

	Biotech	Pharma	**Question 1** Alzheimer's Existing Infrastructure	**Question 2** Alzheimer's Improved Infrastructure
Phase 1 to 2	0.84	0.71	**[.70]**	**[.70]**
Phase 2 to 3	0.56	0.44	**[.50]**	**[.40]**
Phase 3 to approval	0.64	0.69	**[.20]**	**[.50]**
Phase 2 to approval	**0.36**	**0.30**	**[.10]**	**[.20]**
Phase 1 to approval	**0.30**	**0.21**	**[.07]**	**[.14]**

Table 3. Cycle times (months from start of Phase to start of next Phase)

	Biotech	Pharma	**Question 1** Alzheimer's Existing Infrastructure	**Question 2** Alzheimer's Improved Infrastructure
Preclinical	52.0	52.0	**[52]**	**[52]**
Phase 1	19.5	12.3	**[12]**	**[12]**
Phase 2	29.3	26.0	**[26]**	**[26]**
Phase 3	32.9	33.8	**[48]**	**[40]**
Regulatory Review	16.0	18.2	**[18]**	**[18]**
Total	**149.7**	**142.3**	**[156]**	**[144]**

Question 3 If in Table 3 you indicated a change in cycle time for preclinical, Phase 1, Phase 2, or Phase 3, would this imply a change in the average cost of taking a drug candidate through the Phase? Y/N If yes, would that change be proportional to the change in cycle time (e.g. half the time implies half the cost), or more/less than proportional? Please explain. [ ]

C. Changes in Alzheimer's R&D performance

What would happen to private investment in Alzheimer's R&D in the new environment with the recommended infrastructure?

Question 4 Would companies that are currently pursuing Alzheimer's R&D plan to invest

[ ] less OR [ ] more OR [ ] about the same

in the new environment with the recommended infrastructure?

If less or more, roughly what percent? **[ ]**

Question 5 Taking into account how companies that are NOT currently pursuing Alzheimer's R&D might respond, would TOTAL planned investment in Alzheimer's R&D be

[ ] less OR [ ] more OR [ ] about the same

in the new environment with the recommended infrastructure?

If less or more, roughly what percent? **[ ]**

D. Acceleration of disease-modifying therapies for Alzheimer's

In this section, we ask about the likelihood of having – by 2025 – therapies approved that slow the progression of Alzheimer's so that onset of dementia (conversion from mild cognitive impairment to dementia) is delayed

- by **at least two years** and by **at least 5 years** and
- in **at least 50% of cases** and in **at least 75% of cases**.

Note: We are asking about your perception of the probability of achieving these targets based on the effectiveness of **any** drug or combination of drugs making it to market—not necessarily drugs developed by your company.

Question 8 Please provide estimates of the probabilities in the table below:

By 2025, delay onset of dementia	Probability with existing infrastructure	Probability with the recommended infrastructure
by at least **2 years** in at least **50%** of cases	[ ]	[ ]
by at least **5 years** in at least **50%** of cases	[ ]	[ ]
by at least **5 years** in at least **75%** of cases	[ ]	[ ]

Thank you again for the time and thought you have put into answering our questions. We look forward to sharing the results of our study with you.

Appendix B: Reducing the Cost of Alzheimer's Disease Drug Development

The expected cost of developing a new drug is calculated by summing the risk-adjusted, capitalized cost of each Phase of development, which is calculated using the following formula. Parameters in the formula are defined in Table B-1. Capitalization assumes continuous compounding at the annual interest rate r, which is set at the 11% real cost of capital for the biopharmaceutical industry (Harrington, 2012).

$$\left(c\int_{t_{end}}^{t_{start}} e^{rt/12}\,dt\right)/p = \left(\frac{c}{p}\right)\left(\frac{12}{r}\right)\left(e^{rt_{start}/12} - e^{rt_{end}/12}\right)$$

Table B-1. Parameters Characterizing Each Phase of Drug Development

Parameter	Description
t_{start}	Time in months from start of Phase to date of new drug approval
t_{end}	Time in months from end of Phase to date of new drug approval
c	Cost, per month, per compound in Phase
p	Probability that a compound undergoing this Phase of development is ultimately approved for marketing
r	Cost of capital, as an annual interest rate

Tables B-2, B-3, and B-4 illustrate the calculation of the capitalized cost of an Alzheimer's disease (AD) disease-modifying drug, under the existing infrastructure and recommended infrastructure scenarios. The duration, cost, and probability estimates were provided by experts in AD research and drug development. Taking the means of the data they provided for each development Phase, we found the capitalized cost of an AD-modifying therapeutic would be $5,693 million under the current infrastructure and $2,027 million under the recommended infrastructure.

Table B-2. Durations of Drug Development Phases (Months)

Phase	Typical New Drug Mean	Alzheimer's Disease-Modifying: Existing Infrastructure Mean (95% CI)	Alzheimer's Disease-Modifying: Recommended Infrastructure Mean (95% CI)
Preclinical	52.0	50.1 (46.5, 53.8)	49.9 (46.2, 53.5)
Phase I	12.3	12.8 (11.7, 13.9)	12.6 (11.7, 13.5)
Phase II	26.0	27.7 (24.6, 30.9)	25.2 (23.0, 27.4)
Phase III	33.8	50.9 (48.7, 53.2)	39.4 (36.2, 42.7)
Regulatory Review	18.2	18.0 (16.9, 19.1)	16.9 (15.0, 18.8)
Total	142.3	159.6 (148.4, 170.8)	144.0 (132.1, 155.9)

Source: The mean for a typical new drug is from DiMasi and Grabowski (2007). Alzheimer's figures are based on interviews with experts in Alzheimer's research. Quantitative answers to these questions were provided by 15 interviewees. Confidence intervals are plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

Table B-3. Average Transition Probabilities

Transition	Typical New Drug	Alzheimer's Disease-Modifying: Existing Infrastructure Mean (95% CI)	Alzheimer's Disease-Modifying: Recommended Infrastructure Mean (95% CI)
Phase I to II (1)	0.71	0.67 (0.63, 0.70)	0.69 (0.67, 0.71)
Phase II to III (2)	0.44	0.47 (0.43, 0.51)	0.42 (0.41, 0.43)
Phase III to Approval (3)	0.68	0.24 (0.16, 0.34)	0.58 (0.47, 0.68)
Phase II to Approval (2)×(3)	0.30	0.11 (0.08, 0.15)	0.24 (0.20, 0.29)
Phase I to Approval (1)×(2)×(3)	0.21	0.07 (0.05, 0.09)	0.16 (0.14, 0.19)
Ratio of Phase II failures to total failures in Phase II and III combined	0.80	0.60 (0.53, 0.66)	0.77 (0.73, 0.80)

Source: The mean for a typical new drug is from DiMasi and Grabowski (2007). Alzheimer's figures are based on interviews with experts in Alzheimer's research. Confidence intervals are plus or minus 1.96 times the standard error (estimated standard deviation of the mean). A full complement of quantitative answers (first three rows, from which the last three rows can be calculated) under both scenarios (existing infrastructure and recommended infrastructure) was provided by 19 interviewees; another 2 interviewees provided only Phase I to II and Phase II to approval estimates for both scenarios; another 2 interviewees provided only Phase I to II and Phase II to approval estimates for existing infrastructure. To obtain a set of averages consistent with one another, the reported average transition probabilities for Phase II to III and Phase III to approval were calculated by using the Phase I to II and Phase II to approval means (based on the greatest number of interviews in each scenario, 23 for existing and 21 for recommended infrastructure) and the mean ratio of Phase II failures to total failures in Phase II and III combined (which is calculated from a subset of 19 interviews).

Table B-4. Average Costs of Drug Development

Phase	Monthly Out-of-Pocket Cost ($ millions per molecule in development)	Typical New Drug Capitalized at 11% ($ millions per new drug approved)	Alzheimer's Disease-Modifying: Existing Infrastructure Capitalized at 11% ($ millions per new drug approved) Mean (95% CI)	Alzheimer's Disease-Modifying: Recommended Infrastructure Capitalized at 11% ($ millions per new drug approved) Mean (95% CI)
Preclinical	0.72	510	1,658 (1,041, 2,872)	642 (440, 969)
Phase I	2.73	338	1,193 (757, 2,039)	458 (323, 673)
Phase II	2.00	312	1,048 (690, 1,714)	387 (279, 555)
Phase III	5.64	385	1,794 (1,203, 2,916)	539 (410, 738)
Total		1,545	5,693 (3,691, 9,541)	2,027 (1,453, 2,935)

Source: Monthly out-of-pocket costs per compound are based on DiMasi and Grabowski (2007) and DiMasi, Hansen, and Grabowski (2003) and adjusted for inflation using the GDP Implicit Price Deflator (U.S. Department of Commerce: Bureau of Economic Analysis, Series ID: GDPDEF). All costs were calculated using the average durations and transition probabilities from Tables B-2 and B-3. Cost lower bounds were calculated using lower-bound durations and upper-bound transition probabilities. Cost upper bounds were calculated using upper-bound durations and lower-bound transition probabilities. The 11% cost is from Harrington (2012).

The estimated costs of developing a disease-modifying drug for AD ($5,693 million with the current infrastructure and $2,027

million with improved infrastructure) are estimates for the industry as a whole, including the cost of all failures by multiple companies that would be expected before one drug is approved for marketing.

The relationship between the perspective of industry and that of an individual company can be better understood by considering the cost of drug development from the perspective of a single drug candidate entering Phase I trials.

Tables B-5 and B-6 develop the $5,693 million and $2,027 million estimates in a different way. The steps are mathematically identical to using the formula illustrated at the beginning of Appendix B, but they are arranged to highlight the expected cost of entering a drug candidate in Phase I trials and then develop the total capitalized cost of one new drug approval.

Table B-5. Cost of AD Disease-Modifying Drug Development with Existing Infrastructure

Eventual Outcome for a Compound Entering Phase I	Out-of-Pocket Cost ($ millions)	Cost ($ millions) Capitalized to Date That Development Stops or Drug is Approved	Present-Value Cost ($ millions) at Date of Phase I Start (11% discount rate)	Probability
Development stops after Phase I	71	89	79	0.33
Development stops after Phase II	126	177	122	0.35
Development stops after Phase III	413	648	280	0.24
Drug is approved	413	765	280	0.07
			Expected present-value cost = $(79 \times 0.33) + (122 \times 0.35) + (280 \times 0.24) + (280 \times 0.07)$	$157 million
			Cost per new drug approval = $157 million divided by 0.07	$2,087 million
			Capitalized to date of drug approval = $2,087 million $\times e^{(109.4)(0.11/12)}$ (Phase I starts an average of 109.4 months prior to approval)	$5,693 million

Notes: (1) Numbers may not exactly replicate because of rounding. For example, $2,087 million comes from dividing approximately $156.5 million by approximately 0.075.

(2) Out-of-pocket cost is the monthly cost for each Phase (Table B-3) times the number of months spent in that Phase (Table B-2):

$$71 = (0.72)(50.1) + (2.73)(12.8)$$

$$126 = 71 + (2.00)(27.7)$$

$$413 = 126 + (5.64)(50.9)$$

(3) Present-value cost is value of costs incurred at the date the drug candidate enters Phase I:

$$79 = \int_{-50.1}^{0} 0.72e^{t(0.11/12)}dt + \int_{0}^{12.8} 2.73e^{t(0.11/12)}dt$$

$$122 = 79 + \int_{12.8}^{12.8+27.7=40.5} 2.00e^{t(0.11/12)}dt$$

$$280 = 122 + \int_{40.5}^{40.5+50.9=91.5} 5.64e^{t(0.11/12)}dt$$

(4) Probabilities are derived from Table B-3 as follows (note that probabilities do not sum to 1 due to rounding): $0.33 = 1 - 0.67$, $0.35 = (0.67)(1 - 0.47)$, $0.24 = (0.67)(0.47)(1 - 0.24)$.

Table B-6. Cost of AD Disease-Modifying Drug Development with Recommended Infrastructure

Eventual Outcome for a Compound Entering Phase I	Out-of-Pocket Cost ($ millions)	Cost ($ millions) Capitalized to Date That Development Stops or Drug is Approved	Present-Value Cost ($ millions) at Date of Phase I Start (11% discount rate)	Probability
Development stops after Phase I	70	87	78	0.31
Development stops after Phase II	121	167	118	0.40
Development stops after Phase III	343	507	250	0.12
Drug is approved	343	592	250	0.17
			Expected present-value cost = $(78 \times 0.31) + (118 \times 0.40) + (250 \times 0.12) + (250 \times 0.17)$	$144 million
			Cost per new drug approval = $144 million divided by 0.17	$855 million
			Capitalized to date of drug approval = $855 million $\times e^{(94.1)(0.11/12)}$ (Phase I starts an average of 94.1 months prior to approval)	$2,027 million

Notes: (1) Numbers may not exactly replicate because of rounding. For example, $855 million comes from dividing approximately $143.5 million by approximately 0.168.

(2) Out-of-pocket cost is the monthly cost for each Phase (Table B-3) times the number of months spent in that Phase (Table B-2):

$$70 = (0.72)(49.9) + (2.73)(12.6)$$

$$121 = 70 + (2.00)(25.2)$$

$$343 = 121 + (5.64)(39.4)$$

(2) Present-value cost is value of costs incurred at the date the drug candidate enters Phase I:

$$78 = \int_{-49.9}^{0} 0.72e^{t(0.11/12)}dt + \int_{0}^{12.6} 2.73e^{t(0.11/12)}dt$$

$$118 = 78 + \int_{12.6}^{12.6+25.2=37.8} 2.00e^{t(0.11/12)}dt$$

$$250 = 118 + \int_{37.8}^{37.8+39.4=77.2} 5.64e^{t(0.11/12)}dt$$

(3) Probabilities are derived from Table B-3 as follows: $0.31 = 1 - 0.69$, $0.40 = (0.69)(1 - 0.42)$, $0.12 = (0.69)(0.42)(1 - 0.58)$.

Appendix C: Reducing Burden of Alzheimer's Disease

Estimates of the future burden of Alzheimer's disease (AD) are based on U.S. population projections by single year of age from the U.S. Census and on the estimated probabilities of having dementia at different ages from Hurd et al. (2013). The future burden of AD is characterized in two ways: first as the number of people with dementia on an annual basis and second as the cost of providing care for those people. The expected near tripling of the number of cases of dementia—from 2.9 million in 2012 to 8.7 million in 2060—is driven by a predicted 140% increase in the U.S. population over the age of 70, with a disproportionate increase in the number of people in the oldest age groups.

Assuming no change in the age-specific probability of dementia, the probability that a typical person over the age of 70 will have dementia increases from 10.9% to 13.5%. Note that the number of cases refers to the total number of people living with dementia in a given year, not the number of newly diagnosed people in a given year.

For this study, estimates of the probability of dementia from Hurd et al. (2013) were converted from 5-year age group estimates to single-year-of-age estimates by an interpolation procedure. Using a functional form suggested by Brookmeyer et al. (2007), we assumed the probability of dementia depends on age according to $\alpha e^{\beta \cdot \mathrm{AGE}}$, where e is the base to the natural logarithms and α and β are constants chosen to be consistent with Hurd et al. (2013) age group probability estimates. These

probabilities were applied to U.S. Census population estimates by single year of age for 2012 through 2060 (U.S. Census, 2012).

Table C-1 presents the estimated number of cases of dementia by age group for 2012 after applying Hurd et al.'s (2013) estimated probabilities to U.S. Census data. Table C-2 presents the results of the interpolation procedure for estimating dementia cases by single year of age. (The rightmost columns of Tables C-1 and C-2 can be compared to see that single-year probability estimates generate results that are consistent with Hurd et al. [2013].)

Table C-1. Cases of Dementia by Age Group, 2012

Age Group	2012 Population	Probability of Dementia, Hurd (2013)	Estimated Population with Dementia
71–74 yr	7,728,716	0.028	216,404
75–79 yr	7,487,387	0.049	366,882
80–84 yr	5,781,364	0.130	751,577
85–89 yr	3,760,561	0.203	763,394
≥90 yr	2,144,224	0.385	825,526
Total	26,902,252	0.109	2,923,783

Source: Population estimates come from the U.S. Census. The estimated probability of dementia for each age group comes from Hurd et al. (2013, Table 1).

Table C-2. Cases of Dementia by Single Year of Age, 2012

Age	2012 Population	Probability of Dementia	Estimated Population with Dementia	Total for Age Group for Comparison
71	2,088,697	0.0232	48,446	
72	1,979,907	0.0263	52,008	216,405
73	1,867,500	0.0297	55,556	
74	1,792,612	0.0337	60,395	
75	1,657,546	0.0382	63,245	
76	1,587,866	0.0432	68,615	
77	1,527,381	0.0489	74,748	366,882
78	1,377,410	0.0554	76,341	
79	1,337,184	0.0628	83,933	
80	1,282,942	0.1067	136,842	
81	1,228,215	0.1179	144,783	
82	1,183,624	0.1303	154,200	751,577
83	1,074,395	0.1440	154,691	
84	1,012,188	0.1591	161,061	
85	930,150	0.1678	156,098	
86	834,342	0.1859	155,070	
87	758,772	0.2058	156,182	763,393
88	666,314	0.2280	151,892	
89	570,983	0.2525	144,151	
90	490,779	0.2796	137,220	
91	409,098	0.3096	126,677	
92	325,568	0.3429	111,647	
93	241,442	0.3798	91,697	
94	194,638	0.4206	81,867	
95	141,801	0.4658	66,054	825,526
96	105,998	0.5159	54,683	
97	77,755	0.5713	44,424	
98	55,076	0.6327	34,849	
99	37,251	0.7008	26,104	
100	64,818	0.7761	50,304	

Source: Population estimates come from the U.S. Census. The estimated probability of dementia for each year is given by $\alpha e^{\beta \cdot \mathrm{AGE}}$, where α equals 3.374×10^{-6} for ages 71–79, 3.578×10^{-5} for ages 80–84, and 2.859×10^{-5} for ages 85–100, and β equals 0.1244 for ages 71–79, 0.1000 for ages 80–84, and 0.1021 for ages 85–100.

Having estimates of the number of cases of dementia by single year of age allows us to simulate the effect of delaying the onset of dementia. To simulate the effect of delaying the onset of dementia by 2 years for 50% of cases, we applied to 50% of the population the probability of dementia for people 2 years younger. For example, half of all 78-year-olds would face the probability of dementia faced by 76-year-olds.

Figure C-1 projects the number of cases of dementia in the United States under four scenarios:

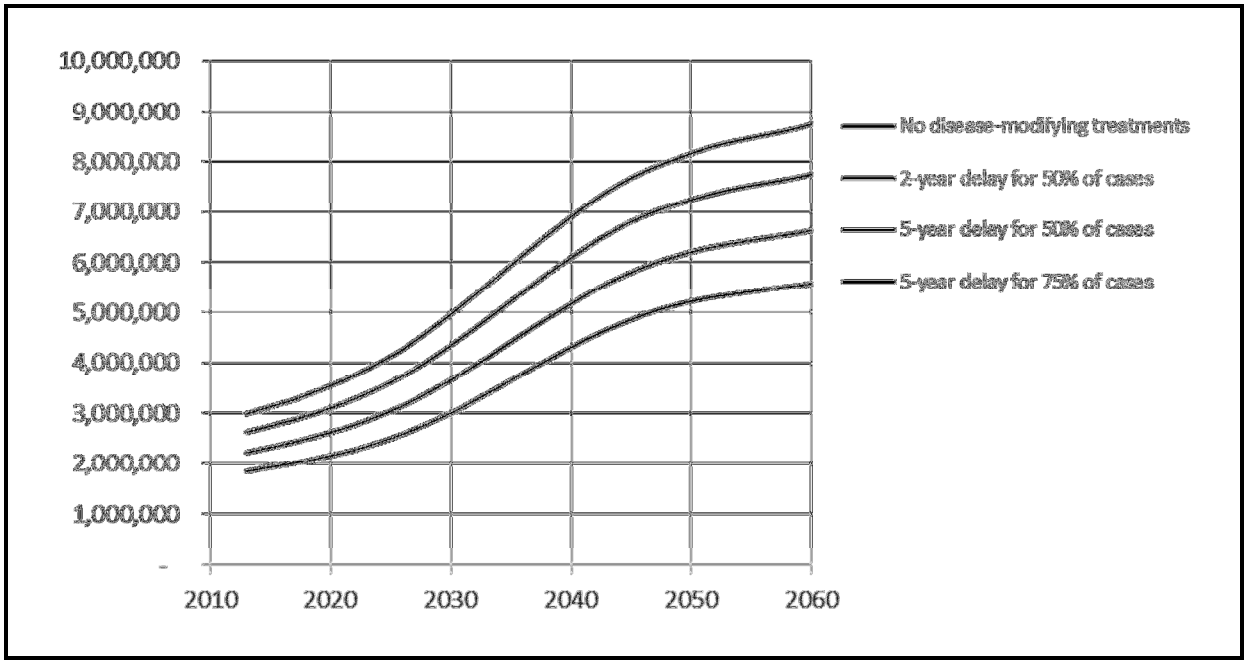
Scenario 1—No disease-modifying treatments. The probabilities in Table C-2 were applied to U.S. Census population projections, showing the number of cases increasing from 2.9 million in 2012 to 8.7 million in 2060 as discussed above.

Scenario 2—Two-year delay for 50% of cases. For half of the population, the probabilities in Table C-2 were shifted by 2 years: 71- and 72-year-olds face no probability of dementia, 73-year-olds face a 0.0232 probability of dementia instead of 0.0297, etc. Under this scenario, the number of cases of dementia is 11% lower in 2060.

Scenario 3—Five-year delay for 50% of cases. For half of the population, the probabilities in Table C-2 were shifted by 5 years: 71- to 75-year-olds face no probability of dementia, 76-year-olds face a 0.0232 probability of dementia instead of 0.0432, etc. Under this scenario, the number of cases of dementia is 24% lower in 2060.

Scenario 4—Five-year delay for 75% of cases. For 75% of the population, the probabilities in Table C-2 are shifted by 5 years: 71- to 75-year-olds face no probability of dementia, 76-year-olds face a 0.0232 probability of dementia instead of 0.0432, etc. Under this scenario, the number of cases of dementia is 36% lower in 2060.

Figure C-1. Projected Cases of Dementia in the United States



Note: The rising number of cases is driven by the increasing population over 70 years of age in the United States. Age-specific probabilities of dementia are held constant over time.

The expected number of cases of dementia in a future year depends on the probability of developing disease-modifying treatments. Take the year 2030 in Figure C-1 as an example. Only if one believes that there is zero probability of being able to delay—by any amount—the onset of dementia by 2030 would one expect there to be 5 million cases of dementia in the United States in 2030. If instead one believed that we would be able to delay the onset of dementia by 5 years in 75% of cases by 2030, then one would expect there to be 3 million cases of dementia in 2030.

Under uncertainty about our ability to alter the course of AD by any future year, it is appropriate to view the expected number of cases of dementia in a given year as a probability-weighted average of all possible treatment scenarios. To have a tractable problem, we have focused on just three treatment scenarios: those discussed above and illustrated in Figure C-1.

The three scenarios are ordered: Achieving *at least* a 5-year delay for 75% of cases (where *at least* applies to both the delay and the percent of cases) implies *at least* a 5-year delay for 50% of cases, which in turn implies *at least* a 2-year delay for 50% of cases. Trivially, any treatment scenario implies *at least* a delay by zero years for 0% of cases. The probabilities of these events are ordered as follows:

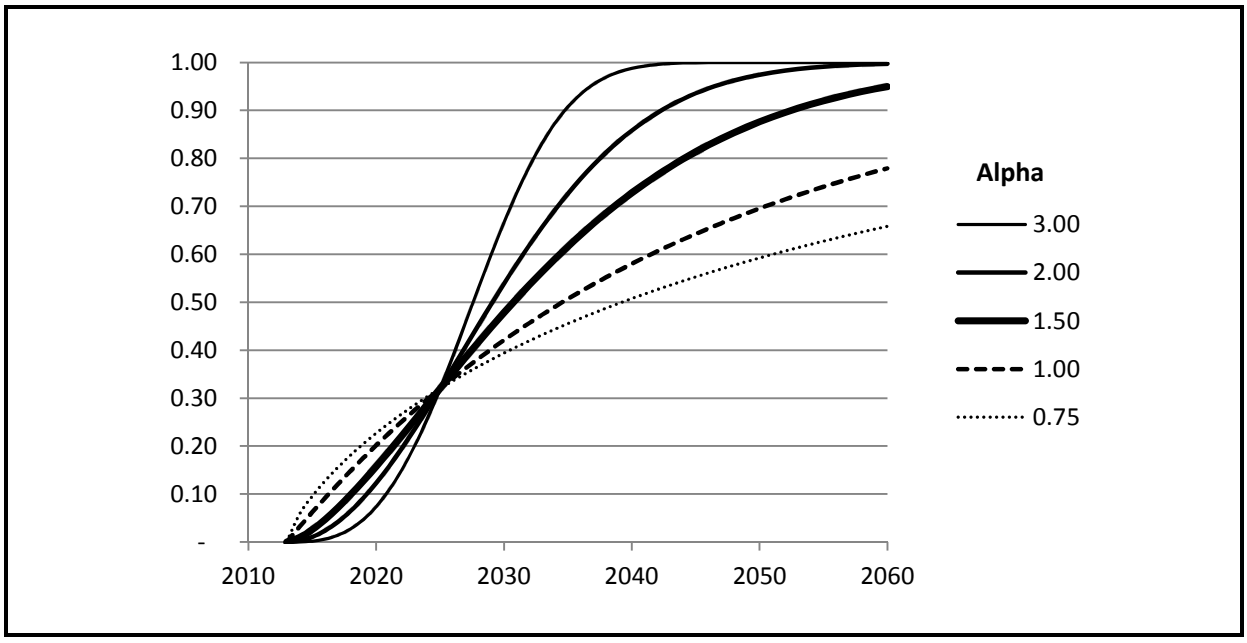
$$1 = \Pr(\geq 0 \text{ yr delay for } 0\%) > \Pr(\geq 2 \text{ yr delay for } 50\%) > \Pr(\geq 5 \text{ yr delay for } 50\%) > \Pr(\geq 5 \text{ yr delay for } 75\%)$$

The time until each scenario is achieved is assumed to follow a Weibull distribution. The probability of having achieved a given scenario by a given time t is therefore given by the cumulative Weibull distribution function $1 - e^{-(t/\beta)^{\alpha}}$, where β determines how quickly the probability accumulates (the larger is β the more slowly the probability accumulates) and α determines the shape of the distribution. For values of α less than 1 (equal to 1; greater than 1), the distribution describes a process where the probability of the scenario being achieved in a given interval of time is decreasing (constant; increasing) as time goes on.

For describing the time until a treatment scenario is achieved, it seems appropriate to consider values for $\alpha \geq 1$, because the

knowledge accumulated through ongoing research and drug development efforts can be applied to improve tools and methods. Values for $\alpha < 1$ could describe a situation in which, if a treatment is not developed within a certain timeframe, it is less likely to be pursued going forward. This situation might be appropriate to describe the development of a compound from a particular class, but it is less likely to describe the development of *any* compound that achieves a given treatment scenario. Figure C-2 illustrates a number of cumulative Weibull distributions passing through probability 0.32 in the year 2025.

Figure C-2. Weibull Distributions



For any given choice of α, the value of β is chosen to reflect experts' predictions, summarized in Table C-3. For example, to parameterize the Weibull distribution for "at least a 2-year delay for 50% of cases," with existing infrastructure, β is chosen such that $1 - e^{-((2025-2013)/\beta)^{\alpha}} = 0.32$. The metric we are interested in—the number of avoided case-years of dementia attributable to improved infrastructure—turns out to be relatively insensitive to the choice of α. (We will return to this point later in the appendix.)

Table C-3. Probability of Delaying Onset of Dementia by 2025 (Reproduces Table 3-4)

Treatment Scenario	Probability With Existing Infrastructure Mean (95% CI)	Probability With Recommended Infrastructure Mean (95% CI)	Difference in Probability Mean (95% CI)
At least a 2-year delay for 50% of cases	0.32 (0.22, 0.42)	0.49 (0.39, 0.59)	0.17 (0.11, 0.23)
At least a 5-year delay for 50% of cases	0.16 (0.09, 0.23)	0.31 (0.22, 0.40)	0.15 (0.10, 0.20)
At least a 5-year delay for 75% of cases	0.05 (0.02, 0.07)	0.12 (0.07, 0.17)	0.07 (0.04, 0.11)

Note: CI refers to confidence interval.

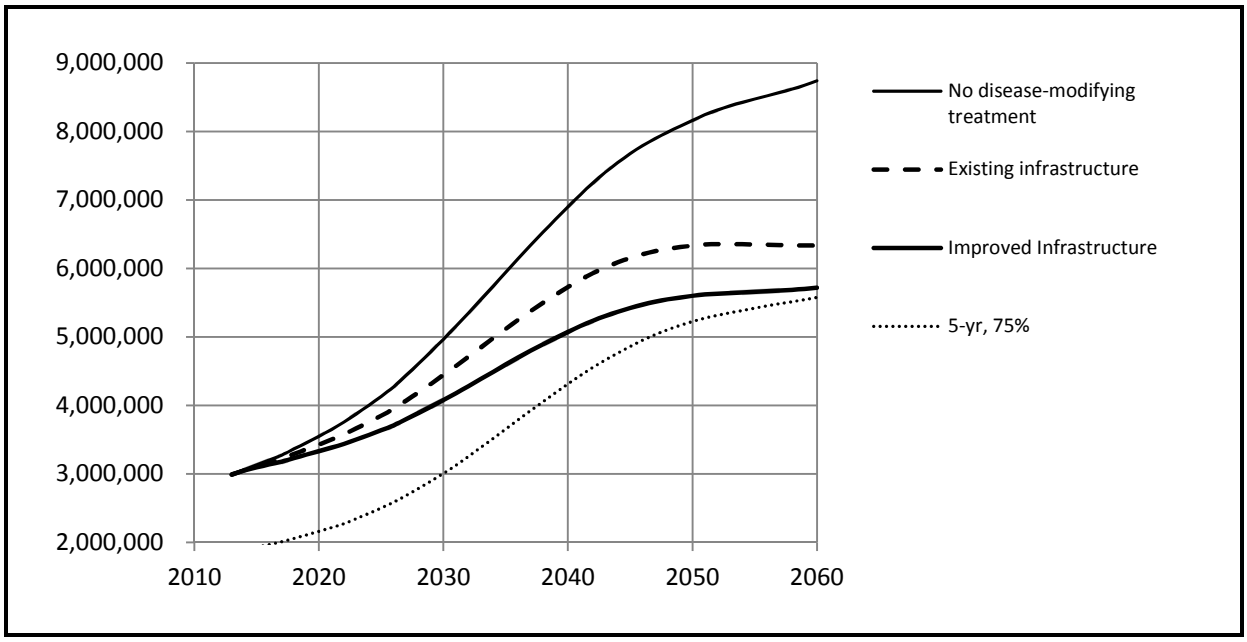
Source: Probability estimates were obtained from interviews with experts in Alzheimer's research. Answers for 2-year and 5-year delay in 50% of cases were provided by 17 interviewees. Answers for 5-year delay in 75% of cases were provided by 12 interviewees. Confidence intervals are plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

Having parameterized a Weibull distribution for each treatment scenario for a given situation (e.g., existing or improved infrastructure, upper or lower bound estimate), the probability-weighted average of the treatment scenarios is constructed for each year as follows. We will use the probabilities in the first column of Table C-3 to illustrate.

Taking 0.32 as the probability of at least a 2-year delay for 50% of cases, we assigned the complementary probability 0.68 to the scenario with no disease-modifying treatment. Then taking 0.16 as the probability of at least a 5-year delay for 50% of cases, we assigned the probability (0.32 – 0.16 equals) 0.16 to the scenario with exactly a 2-year delay in exactly 50% of cases. Likewise (referring to the probabilities 0.16 and 0.05 in the first column of Table C-3), we assigned the probability (0.16 – 0.05 equals) 0.11 to the scenario with exactly a 5-year delay in exactly 50% of cases. Finally, we assigned the probability 0.05 to the scenario with exactly a 5-year delay in exactly 75% of cases.

Recall that Figure C-1 projected the number of cases of dementia in the United States under each of the treatment scenarios. Figure C-3 projects the expected number of cases with the existing infrastructure and with improved infrastructure. Projections are based on probability-weighted averages of the treatment scenarios, constructed as described above. The Weibull distributions use $\alpha = 1.25$ for the 2-year/50% scenario, $\alpha = 1.58$ for the 5-year/50% scenario, and $\alpha = 2.23$ for the 5-year/75% scenario.

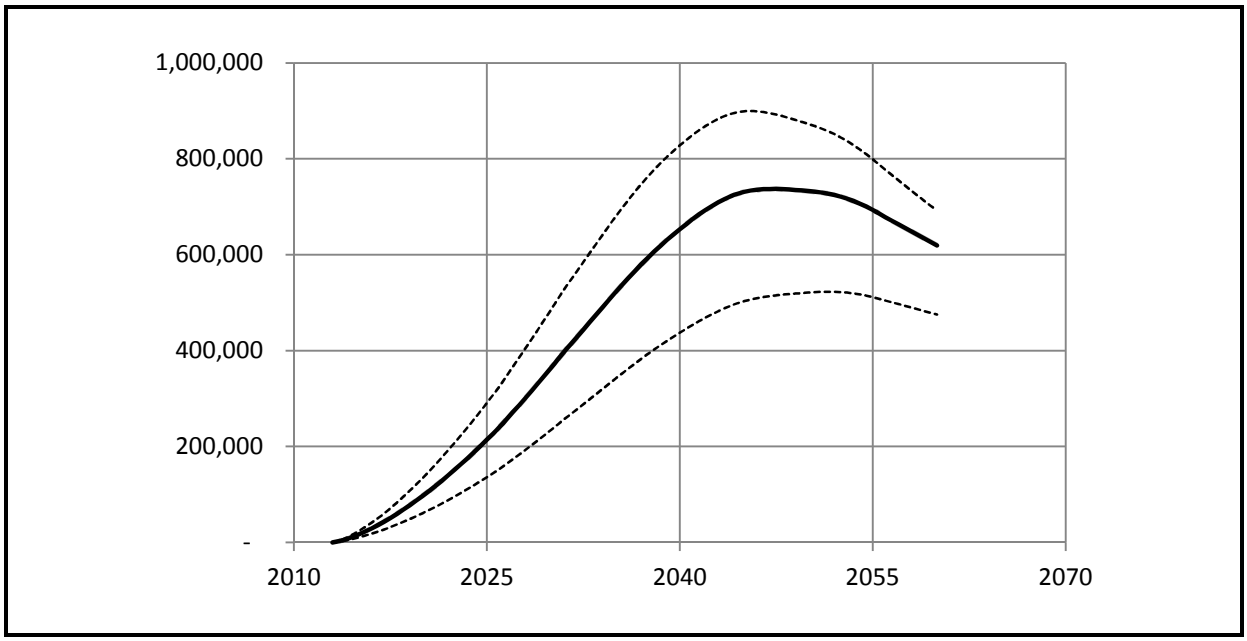
Figure C-3. Expected Number of Cases of Dementia in the United States



Note: The Weibull distributions underlying these projections use $\alpha = 1.25$ for the 2-year/50% scenario, $\alpha = 1.58$ for the 5-year/50% scenario, and $\alpha = 2.23$ for the 5-year/75% scenario.

Figure C-4 shows the number of avoided cases of dementia corresponding to the projections in Figure C-3—the difference between the projection with existing infrastructure and that with improved infrastructure. Note that these are the numbers of avoided cases on an annual basis, or avoided case-years. Dashed lines indicate confidence intervals based on the rightmost column of Table C-3. The total number of avoided cases from 2025 to 2040 is 7.0 million cases with a confidence interval of 4.6 million to 9.2 million cases.

Figure C-4. Avoided Case-Years of Dementia Attributable to Improved Infrastructure



Note: The Weibull distributions underlying these projections use $\alpha = 1.25$ for the 2-year/50% scenario, $\alpha = 1.58$ for the 5-year/50% scenario, and $\alpha = 2.23$ for the 5-year/75% scenario.

The estimates in Section 3 combined two parameterizations of the Weibull distributions. The first used $\alpha = 1.00$ for the 2-year/50% scenario, $\alpha = 1.35$ for the 5-year/50% scenario, and $\alpha = 1.95$ for the 5-year/75% scenario. The second used $\alpha = 1.50$ for the 2-year/50% scenario, $\alpha = 1.80$ for the 5-year/50% scenario, and $\alpha = 2.50$ for the 5-year/75% scenario. These alternative parameterizations were combined by averaging the point estimates and taking the widest of their respective upper and lower bounds, year by year. This resulted in a point estimate of total avoided cases from 2025 to 2040 of 7.0 million cases and a confidence interval of 4.4 million to 9.4 million cases. The confidence intervals shown in Figure 3-2 are wider than those in Figure C-4 although the point estimates are very similar.

Table C-4 makes the point that as long as we restrict attention to the number of cases avoided from 2025 to 2040, estimates are relatively insensitive to the choice of α. The variation resulting from the choice of α is small in comparison to the variation in experts' opinions as reflected in the confidence intervals.

Table C-4. Sensitivity of Estimates to Weibull α

Weibull α			Avoided Cases (millions), Mean (95% CI)	
2-yr/50%	5-yr/50%	5-yr/75%	2025–2040	2025–2060
0.75	1.13	1.68	6.37 (4.11, 8.48)	21.48 (14.23, 27.60)
1.00	1.35	1.95	6.74 (4.37, 8.89)	21.86 (14.81, 27.47)
1.25	1.58	2.23	7.04 (4.60, 9.21)	21.07 (14.63, 25.88)
1.50	1.80	2.50	7.28 (4.80, 9.42)	19.2 (13.66, 23.14)
1.75	2.03	2.78	7.42 (4.94, 9.50)	16.68 (12.10, 19.86)
2.00	2.25	3.05	7.45 (5.02, 9.44)	14.08 (10.32, 16.69)
2.25	2.48	3.33	7.38 (5.02, 9.24)	11.8 (8.66, 13.99)
2.50	2.70	3.60	7.19 (4.95, 8.91)	9.98 (7.31, 11.86)

Note: CI refers to confidence interval.

Table C-5 shows the number of avoided cases of dementia from 2025 to 2040 corresponding to the projections in Figure 3-2. Recall that these are similar to what is shown in Figure C-4, but with wider confidence intervals to account for uncertain α. Table C-5 then shows the present discounted value of these avoided cases, using 3% and 7% discount rates and valuing an avoided case-year at $41,689 and $56,290, following Hurd et al. (2013). The lower estimate of cost of care uses the valuation of family members' forgone wages to estimate the contribution of informal care to total cost; the higher estimate uses the replacement cost, meaning the cost of hiring a caregiver to provide the services performed by family members.

Limitations

The values suggested by Hurd et al. (2013) are costs of care and do not reflect the full disutility of the disease, both to the person with dementia and to that person's family, friends, and community. The cost incurred to care for a condition is a lower bound on the value of avoiding the condition. Therefore, our approach may tend to underestimate the value of accelerating the development of disease-modifying treatments.

We have not attempted to account for longer life expectancy resulting from delay of the onset of dementia. Recognizing that portion of "avoided" case years may be only postponed, our approach may tend to overestimate the impact on cost of care. Still, each year that the onset of dementia is postponed is a year of relatively independent function reclaimed, and the

utility of one such year reclaimed can reasonably be expected to exceed the monetary cost of caring for someone who has lost the ability to function independently. On balance, we are of the opinion that our approach is more likely to lead to an underestimation of the full social value of accelerating the development of disease-modifying treatments.

Table C-5. Avoided Cases of Dementia and Present Discounted Value

		Present Discounted Value of Avoided Cases ($ billions)			
Year	**Avoided Cases (thousands), Mean (95% CI)**	**$41,689 per Case-Year, Discounted at 7%**	**$56,290 per Case-Year, Discounted at 7%**	**$41,689 per Case-Year, Discounted at 3%**	**$56,290 per Case-Year, Discounted at 3%**
2025	216 (135, 297)	3.99 (2.50, 5.50)	5.39 (3.37, 7.43)	6.30 (3.94, 8.69)	8.51 (5.33, 11.73)
2026	243 (152, 334)	4.21 (2.63, 5.78)	5.68 (3.55, 7.81)	6.90 (4.32, 9.49)	9.32 (5.83, 12.81)
2027	272 (170, 374)	4.4 (2.74, 6.05)	5.94 (3.70, 8.17)	7.50 (4.68, 10.32)	10.12 (6.31, 13.93)
2028	302 (187, 417)	4.57 (2.83, 6.30)	6.16 (3.82, 8.51)	8.08 (5.01, 11.16)	10.92 (6.76, 15.06)
2029	333 (206, 461)	4.71 (2.90, 6.50)	6.36 (3.92, 8.78)	8.66 (5.34, 11.97)	11.69 (7.21, 16.16)
2030	365 (224, 504)	4.81 (2.96, 6.65)	6.50 (4.00, 8.97)	9.20 (5.66, 12.70)	12.42 (7.64, 17.15)
2031	396 (243, 546)	4.88 (3.00, 6.73)	6.59 (4.05, 9.09)	9.70 (5.96, 13.36)	13.09 (8.04, 18.04)
2032	427 (262, 587)	4.92 (3.02, 6.76)	6.65 (4.08, 9.13)	10.16 (6.24, 13.95)	13.71 (8.42, 18.84)
2033	458 (282, 626)	4.94 (3.04, 6.75)	6.66 (4.10, 9.11)	10.58 (6.50, 14.45)	14.28 (8.78, 19.51)
2034	488 (301, 663)	4.92 (3.03, 6.68)	6.64 (4.09, 9.01)	10.94 (6.75, 14.86)	14.78 (9.11, 20.06)
2035	517 (321, 695)	4.86 (3.02, 6.54)	6.57 (4.07, 8.83)	11.24 (6.98, 15.12)	15.18 (9.42, 20.42)
2036	545 (340, 726)	4.79 (2.99, 6.39)	6.47 (4.04, 8.62)	11.51 (7.18, 15.34)	15.54 (9.69, 20.71)
2037	571 (359, 754)	4.70 (2.95, 6.20)	6.34 (3.98, 8.37)	11.72 (7.36, 15.46)	15.82 (9.94, 20.88)
2038	596 (378, 778)	4.58 (2.90, 5.98)	6.19 (3.92, 8.07)	11.88 (7.52, 15.50)	16.03 (10.15, 20.93)
2039	619 (396, 801)	4.45 (2.84, 5.75)	6.00 (3.84, 7.77)	11.98 (7.65, 15.49)	16.17 (10.33, 20.92)
2040	640 (413, 823)	4.30 (2.77, 5.52)	5.80 (3.74, 7.46)	12.02 (7.76, 15.45)	16.23 (10.48, 20.86)
Total	6,990 (4,369, 9,386)	74.02 (46.13, 100.08)	99.96 (62.28, 135.16)	158.36 (98.84, 213.30)	213.83 (133.46, 288.01)

Note: CI refers to confidence interval. Present discounted value for a given year y is $V \cdot N \cdot (1+r)^{2013-y}$, where V is the monetary value associated with an avoided case ($41,689 or $56,290), N is the number of avoided cases, and r is the discount rate (0.07 or 0.03).

